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HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

TREATMENT WITH A CORN-OIL DIET

BY

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There is much epidemiological evidence for an association between ischaemic heart disease, blood lipids, and dietary factors (Bronte-Stewart, 1959a, 1959b). Fat is the important constituent of the diet in the regulation of blood lipids (Ahrens, 1957), and dietary cholesterol has little influence on the blood level (Keys *et al.*, 1950). Keys (1952) thought that the major factor was the total amount of fat in the diet. Kinsell *et al.* (1952) showed that vegetable fat compared with an isocaloric amount of animal fat produced a significant fall in the blood lipids when fed to normal people.

In 1955 Kinsell and Michaels showed that there was a direct relation between the unsaturated-fatty-acid content of the diet and the effect on blood lipids, which was confirmed by Ahrens *et al.* (1955), Beveridge *et al.* (1955), and Bronte-Stewart *et al.* (1956). Kinsell and Sinclair (1957) postulated that the depressant effect on the serum lipids was due to the essential fatty-acid content, particularly linoleic acid, but this is unlikely (Ahrens *et al.*, 1959).

Other methods have been used to depress the blood lipids. Sitosterol, derived from plant sterols, in high dosage has a temporary effect (Barber and Grant, 1955; Leonard, 1956). Heparin has been used to lower the

blood cholesterol (Calvert, 1953; Soffer and Murray, 1954), but requires prolonged systemic administration and is not without danger. Oestrogens lower the blood cholesterol in hypercholesterolaemic men with coronary artery disease (Oliver and Boyd, 1954), but the unpleasant side-effects, especially feminization, may preclude its extensive trial. Similarly, nicotinic acid in very high dosage depresses the blood lipids in hypercholesterolaemia (Parsons *et al.*, 1956; Galbraith *et al.*, 1959). The effect is small and the side-reactions of the drug may be severe. It is not proposed to examine these methods further in this trial.

Familial hypercholesterolaemic xanthomatosis is a disorder characterized by xanthomata of skin and tendon with raised blood cholesterol and phospholipids (Thannhauser, 1958). The triglycerides (neutral fats) are normal or only slightly elevated. In the related disorder with xanthomata, idiopathic hyperlipaemia, the triglycerides are greatly increased. In hypercholesterolaemic xanthomatosis there is a high incidence of atherosclerosis and ischaemic heart disease (Fox, 1879; Müller, 1939; Cook *et al.*, 1947; Rigdon and Willeford, 1950; Barr *et al.*, 1954). Atherosclerosis is also common in idiopathic hyperlipaemia (Malmros *et al.*, 1954; Soffer and Murray, 1954; Martt and Connor, 1956), although the contrary view is held by Thannhauser (1958).

In attempts to lower the blood cholesterol by dietary modifications, little attention has previously been paid to the patient. Most experiments have been conducted in metabolic wards with formula feeds which are uninteresting, unpalatable, and impractical for patients carrying on a normal life. Observations have been made on changes in the blood lipids, and there is a tendency for the assessment of clinical improvement to be of secondary importance. This is not unexpected, for the investigations have been mainly concerned with the relation of the blood lipids to ischaemic heart disease. Improvement after any biochemical change is likely to take some time before the benefit may be assessed. A palatable diet is then of importance if such experiments are to be continued for some years. Such a diet containing a high proportion of unsaturated fat derived from corn (maize) oil was used in this study. The oil was given in the form of a "margarine," "milk," and "cheese," with supplements of oil for culinary purposes. The patients had familial hypercholesterolaemic xanthomatosis or idiopathic hyperlipaemia in which the incidence of atherosclerosis is high. Observations were made on the management of this diet and the biochemical response was followed during the treatment and a control period.

Material and Methods

Patients Studied

16 patients from 11 families with hypercholesterolaemic xanthomatosis were investigated. One of them ceased to attend half-way through the trial, and another, a girl aged 17, died from myocardial infarction before the treatment began. Three additional patients with idiopathic hyperlipaemia and one with hypercholesterolaemia but no xanthomata were studied.

The clinical manifestations are shown in Table I. All but one of the patients had xanthoma tendinosum or xanthoma tuberosum. The site of these was recorded and the size of each measured with callipers. Measurement was repeated at the end of the control and treatment periods. The numbers which had increased,

decreased, or remained the same in size in the two periods were compared. The effect of the diet on the xanthomata could then be assessed. Four of the patients had xanthelasma palpebrum, and these were similarly measured. Ten patients had an arcus senilis, the extent of which was recorded.

Six of the patients had angina pectoris. The severity of this was graded clinically into four groups by the method of Wood (1956). Grade 1 was the least affected and grade 4 the most incapacitated. An electrocardiogram was taken at rest and at the beginning and end of the control and treatment periods. Four of the six patients with angina had electrocardiographic evidence of ischaemia.

Six of the patients suffered from intermittent claudication. This was also assessed clinically and graded according to the method of Boyd (1954). Grade 1 was the least severe and grade 3 the most. To assist in the grading an exercise-tolerance test was performed at the beginning and end of the control and treatment periods. In this the patient walked at 4 m.p.h. on the flat, and the distance that he could walk before pain slowed or stopped him was measured. A radiograph of the soft tissues of the leg was taken of all patients for evidence of vessel calcification. This was repeated after treatment.

Four patients were hypertensive. The blood-pressure was recorded in the same arm in the reclining position at each visit. One patient (Case 12) with hypertension had a hemiparesis and some intellectual impairment as a result of cerebrovascular disease. A chest radiograph was taken of all patients. There was evidence of left ventricular enlargement in one patient with hypertension. The presence of atherosclerosis, though difficult to judge, was assessed on the condition and patency of the peripheral vessels and those of the fundus.

Two patients were found to have glycosuria. One of them (Case 14) had a fasting blood-sugar of 222 mg./100 ml. There has been no subsequent glycosuria and blood-sugar levels are normal. The glycosuria in the other patient (Case 6) was found to be due to a low renal threshold. Gout is sometimes confused with this condition, but in all patients the blood uric acid was normal.

All the patients remained at work. They attended the out-patient clinic at monthly intervals and more often when a change of diet was made. Each patient was treated with the diet for four to five months and

observed during a control period of the same length on a normal diet. The patients were divided into a complicated group with angina or intermittent claudication, and an uncomplicated group. Patients in the two groups were allocated randomly to either the treatment followed by control or vice versa.

Diet

All patients were interviewed by a dietitian and details of their normal diet obtained. During the control period this diet was maintained. During the treatment period the equivalent of approximately 100 g./day of corn oil (Table II) was given as "margarine," "milk," "cheese," and oil. As only corn-oil dairy products were used in substitution for all the fats normally eaten it was found

TABLE II.—Effect of Corn-oil Diet on Mean Total Cholesterol (T.C.) and Body Weight in 18 Patients

Case No.	Control Period				Dietary Period						Change in T.C. as % of Control
	Duration (Weeks)	Fat (g./Day)	Weight (kg.)	Mean T.C. (mg./100 ml.)	Duration (Weeks)	Corn Oil (g./Day)	% of Calories	Weight (kg.)	Mean T.C. (mg./100 ml.)		
1	20	56	50	492	22	82	47	50	455	-7	
2	27	71	64	465	23	91	50	66	387	-17	
3	23	99	65	541	23	101	42	61	369	-32	
4	18	125	52	263	19	108	37	50	283	+7	
5	18	90	55	574	19	80	29	52	492	+14	
6	22	133	87	401	22	112	39	86	324	-19	
7	22	132	67	328	18	110	31	68	257	-21	
8	25	71	56	419	18	95	46	55	343	-18	
9	20	108	81	448	19	111	42	79	386	-14	
10	19	89	52	448	20	100	45	52	320	-29	
11	20	78	64	491	19	104	46	64	325	-14	
12	24	—	65	431	24	99	—	65	349	-19	
13	23	67	73	211	21	112	55	74	166	-21	
14	15	69	73	296	17	131	88	71	226	-24	
15	21	142	79	297	23	106	36	76	237	-20	
16	18	154	75	477	19	120	33	70	283	-41	
17	19	72	80	521	19	102	65	80	341	-34	
18	17	173	64	365	18	100	24	61	149	-59	

Mean change in T.C., -23%; S.E., 3.3; P, <0.001.

P=Probability of a mean change at least as big as that observed if the treatment were ineffective.

that 100 g./day was as much as most patients could tolerate. In these products unhydrogenated corn oil replaces the milk and butter fats. The milk contains 20 g./pint (568 ml.) of corn oil, margarine 18 g./oz. (28 g.), and the cheese 5 g./oz. (28 g.). All other fat was eliminated from the diet apart from that contained in protein, 100 g./day of which was allowed. The body weight and calorific value of the diet were kept constant by adjustment of the carbohydrate content.

TABLE I.—Clinical Manifestations (Cases 1-15 had familial hypercholesterolaemic xanthomatosis. Cases 16-18 had idiopathic hyperlipaemia)

Case No.	Age and Sex	Xanthomata				Arcus Senilis	Angina		Intermittent Claudication		Blood-pressure	Atherosclerosis
		Age Onset	Xt	Xu	Xl		Age Onset	Grade	Onset Age	Grade		
1	54 F	29	+	+	+	+	45	2	53	2	120/60	+
2	42 F	32	+	+							170/100	+
3	15 F	14	+								105/80	
4	16 F	14	+								100/60	
5	34 F	23	+		+	+					135/80	
6	40 M	21	+	+							105/70	+
7	47 M	32	+			+	44	1			125/90	+
8	59 F	55	+			+	45	3			155/105	+
9	38 M	c. 16	+			+					115/70	+
10	53 F	c. 16	+			+					125/70	+
11	54 F	45	+			+					130/80	+
12	33 M	33		+		+			29	2	160/115	+
13	41 M	40		+		+					100/60	
14	60 M	45		+	+		47	1	52	3	145/80	+
15	57 M	—					47	1	55	2	125/75	+
16	43 M	32		+		+			32	2	140/100	+
17	61 F	54	+	+		+	59	2	59	3	140/80	+
18	32 M	31		+							100/65	

Xt=Xanthoma tendinosum. Xu=Xanthoma tuberosum. Xl=Xanthelasma. Grade 1 to 4, increasing severity.

Biochemical Methods

Venous blood was taken two to three hours after a fat-free breakfast: 9 ml. of blood was added to 1 ml. of 3.8% sodium citrate, and plasma separated by centrifuging at 3,500 g for 10 minutes. Cholesterol was estimated at least monthly and the other lipids at the beginning and end of the control and treatment periods. All estimations were done in duplicate.

Cholesterol, total and free, was estimated by the method of Schoenheimer and Sperry (1934) as modified by Hawk *et al.* (1954). The ester cholesterol was hence found by deduction.

Phospholipids were determined by estimation of the phosphorus after digestion with perchloric acid, by a slight modification of the method of Allen (1940) in which the scale of the colorimetric determination was reduced in order to increase the sensitivity of the method. The amount of phospholipid was obtained by multiplying the weight of phosphorus by a factor of 25 (assuming a mean molecular weight of 775 for phospholipids).

Total fatty acids were estimated by a method similar to the one used by Dole (1956) for estimation of unesterified fatty acid, modified by the introduction of a hydrolysis stage (Drysdale and Billimoria, 1960).

Triglycerides were obtained by calculation as follows: triglyceride fatty acid = total fatty acid - the sum of the phospholipid fatty acid and the ester cholesterol fatty acid. Total fatty acids were estimated and the fatty acids of phospholipids and ester cholesterol were calculated. The weight of triglyceride was deduced from the triglyceride fatty acid.

Plasma turbidity was measured on a nephelometer (Evans Electroselenium Ltd.), using the arbitrary standard supplied with the instrument.

Blood-clotting and Fibrinolysis

The tests were carried out two hours after a fat-free meal by Miss Jean E. Drysdale. Blood-clotting by the Russell-viper-venom technique and fibrinolysis were measured by use of the methods described by Billimoria *et al.* (1957, 1959). The normal range for the venom time was $25-35 \pm 2$ seconds. The normal lysis time was $2.0-4.0 \pm 0.1$ hour.

Photographic Methods

The xanthomata, xanthelasma, and arcus senilis were photographed at the beginning and end of the control and the treatment period. This was done using an exact reproducible scale of one to two with colour-reversal material. Changes in size were assessed by examination of the photographs on an illuminated screen. An independent observer made a similar assessment.

Plethysmographic Methods

The peripheral circulation was measured by venous occlusion plethysmography. The apparatus consisted of a water-filled foot plethysmograph at 36° C. Changes in volume of the foot produced a change of water level of approximately 1-2 cm. in a graduated tube attached to the top of the plethysmograph box. The tube was connected to a suitable pressure transducer used in association with an amplifier and pen recorder. In this way the water level and hence the volume changes were recorded continuously. The recorder was calibrated direct by reference to the graduated tube.

The procedure with the patient consisted of measuring: (1) the resting blood flow through the foot, and (2) the maximal blood flow after reactive hyperaemia resulting from 20 minutes' arterial occlusion at the calf. The measurements were made before and after dietary treatment. Normal patients aged 19-71 were examined for comparison, and the maximal flow was found to be 16.4 ± 0.7 ml./100 ml.foot/min.

Results

Tolerance of Diet.—The diet was palatable and well tolerated. Eighteen patients completed the trial, having been on treatment for 17 to 24 weeks. Only one patient withdrew—after 19 weeks on the diet, which he disliked. Supervision had been difficult, as he lived far from the hospital, and he was unable to complete the control period. There was a variation in preference for the "margarine," "milk," or "cheese." The patients rapidly adapted the quantities to suit their own taste, keeping the total amount of corn oil constant. Neat oil was generally disliked, and, where possible, was used only in cooking. At the beginning of treatment some patients had a mild gastro-intestinal disturbance, with flatulence, abdominal discomfort, and diarrhoea. This soon subsided, but it persisted in those patients taking neat corn oil until the amount was reduced. On holiday the patients adhered to the principle of the diet, taking the corn-oil products with them.

Xanthomata.—There was a greater response of xanthoma tuberosum than xanthoma tendinosum to the treatment (Table III). Six of the nine patients with xanthoma tuberosum showed a decrease or prevention

TABLE III.—*Effect of Corn-oil Diet on Clinical Manifestations in 18 Patients*

Case No.	Xanthoma Tendinosum	Xanthoma Tuberosum	Xanthelasma	Arcus Senilis	Angina	Claudication
1	—	0	0	0	0	0
2	—	0				
3	—					
4	0					
5	—		0	0		
6	+	—		0		
7	—			0	+	
8	0			0	0	
9	—			0		
10	0			0		
11	+		+	0		
12		0		0		—
13	—					
14	—		—		0	—
15					0	—
16	—	—		0		0
17		—		0	—	0
18		—				

+, Increased. —, Decreased. 0, Unaltered.

of increase in the size of the xanthomata (probability of obtaining as great a preponderance in favour of the diet is 0.031, which is significant at the 5% level). The changes were pronounced (Fig. 1), and some of the smaller xanthoma tuberosum lesions disappeared. Although the effect on xanthoma tendinosum was not statistically significant, the lesions decreased in seven out of 12 patients. The site of the various xanthomata on the body did not alter the effect of the diet. Xanthelasma lesions showed no significant change in size, though the patients believed them to be flatter and less prominent while they were on the diet. Arcus senilis did not alter in any of the patients.

Myocardial Ischaemia.—Only one patient out of six with angina improved while on treatment (Table III). Clinically her angina had been of grade 2 severity and became grade 1. There was no electrocardiographic

change. On the other hand, one patient had a myocardial infarct a month after starting the diet. His electrocardiogram had shown progressive changes of ischaemia during the control period prior to the dietary treatment. After the infarct his angina was worse by one grade. The remaining four patients with angina did not alter clinically and there was no alteration in the electrocardiogram of three of them. The fourth showed some increase in the ischaemic changes.

Intermittent Claudication.—During the treatment period there was symptomatic improvement in three of the six patients with intermittent claudication. They improved clinically by one grade, and this improvement was confirmed by an exercise test in two of them. One of them had a lumbar sympathectomy three months prior to dietary treatment. The plethysmographic measurement of the maximal reactive hyperaemia provoked by ischaemia of the foot showed no significant improvement in these patients (Table IV). This measurement was believed to be more suitable for comparison of the results than the resting flow, for it is less influenced by environmental factors and more readily reproducible (W. J. H. Butterfield, 1960, personal communication). In the six patients with intermittent claudication the flow was increased by more than 2 ml./100 ml.foot/min. in one, decreased in two, and unaltered in three.

TABLE IV.—Effect of Corn-oil Diet on Maximal Flow in the Foot (Normal 16.4 ± 0.7 ml./100 ml.foot/min.) after Reactive Hyperaemia, Measured Plethysmographically

Case No.	Angina (A) and/or Intermittent Claudication (C)	Maximal Flow (ml./100 ml.foot/min.)		
		Control Period	Dietary Period	Change
1	A C	14.1	14.8	+0.7
2		22.1	17.3	-4.8
3		15.8	14.5	-1.3
4		25.2	21.1	-4.1
6	A	14.8	17.0	+2.2
7		13.0	15.0	+2.0
8		16.2	15.4	-0.8
9		9.2	11.8	+2.6
10	C	20.7	15.8	-4.9
11		16.8	12.4	-4.4
12		7.0	4.2	-2.8
13		11.6	15.5	+3.9
14	A C	5.7	4.4	-1.3
15	A C	16.1	9.5	-6.6
16	C	13.6	11.9	-1.7
17	A C	5.8	9.3	+3.5
18		14.7	14.1	-0.6

Mean change, -1.0; S.E., 0.8; not significant.
+, Increased. -, Decreased.

Blood-pressure.—No change was found in the blood-pressure during the treatment compared with the control period, in the normal or hypertensive patients.

Biochemical Results.—The changes in blood lipids are shown in Tables II and V. There was a considerable normal variation in the blood cholesterol from week to week, and fluctuations were found after holiday or illness, when the strict diet was not possible. On

FIG. 1.—Case 17. Effect on xanthoma tuberosum at the elbow (right above; left, below) of 19 weeks' corn-oil diet (A to B) compared with an equal period on normal diet (B to C).

TABLE V.—Effect of Corn-oil Diet on Blood Lipids in 18 Patients

Case No.	Control Period					Dietary Period					Change as % of Control Value				Change in T.G. mg./100 ml.
	EC	FC	PL	TG	Plasma Turbidity Units	EC	FC	PL	TG	Plasma Turbidity Units	EC	FC	PL	Plasma Turbidity Units	
	mg./100 ml.					mg./100 ml.					EC	FC	PL	Plasma Turbidity Units	
1	434	141	445	Nil	44	328	126	419	Nil	30	-25	-11	-6	-32	—
2	296	111	383	260	28	260	101	318	195	26	-12	-9	-17	-7	-65
3	327	121	388	158	—	238	97	301	122	44	-27	-20	-22	—	-36
4	216	78	246	100	23	220	62	266	69	20	+2	-21	+8	-13	-31
5	414	159	414	81	60	325	144	425	199	52	-21	-9	+3	-13	+118
6	285	109	307	Nil	29	242	88	282	25	24	-15	-19	-8	-17	+25
7	237	91	306	142	27	177	65	238	136	25	-25	-29	-22	-7	-6
8	332	108	361	Nil	27	221	79	303	90	23	-33	-27	-16	-14	+90
9	292	133	407	172	30	306	114	372	219	26	+5	-14	-9	-13	+47
10	396	146	406	116	29	242	76	304	109	22	-39	-48	-25	-24	-7
11	259	141	373	147	28	230	92	278	83	24	-11	-35	-25	-14	-64
12	266	125	358	177	82	172	103	353	—	—	-36	-18	-1	—	—
13	132	48	232	233	166	130	44	190	65	48	-2	-8	-18	-71	-168
14	223	79	380	—	—	165	58	305	340	72	-26	-27	-20	—	—
15	242	66	297	60	63	178	73	266	280	47	-26	+11	-10	-25	+220
16	327	160	513	1,070	154	204	88	319	525	98	-37	-45	-38	-36	-545
17	279	156	467	1,066	152	242	115	368	218	116	-13	-26	-21	-24	-848
18	261	127	308	670	172	113	43	196	87	35	-57	-66	-36	-80	-583
Mean	..	..	..	..	..	..	..	..	..	..	-22	-24	-16	-26	-123
S.E.	..	..	..	..	..	..	..	..	..	..	±3.7	±4.1	±3.0	±5.8	±79.5
P	..	..	..	..	..	..	..	..	..	..	<0.001	<0.001	<0.001	<0.001	N.S.

EC=Ester cholesterol. FC=Free cholesterol. PL=Phospholipids. TG=Triglycerides.

starting the treatment there was a transition period generally of one to three weeks before the cholesterol assumed a "steady state" (Fig. 2). The mean total cholesterol for the control and treatment periods was calculated from the values for this "steady state." The total cholesterol showed a significant mean fall on treatment of 23% of the control level with a range of +7% to -59%. The greatest fall in the total cholesterol was found in patients with idiopathic hyperlipaemia. The other lipids showed a significant response to treatment. The ester cholesterol fell by a mean 22%

FIG. 2.—Case 11. Effect on blood lipids of a corn-oil diet compared with normal diet. x—x Total cholesterol. ●—● Free cholesterol. ▲—▲ Phospholipids. ○—○ Triglycerides.

and the free cholesterol by a mean 24%. The phospholipids fell by 16% and plasma turbidity was diminished by 26%. The changes in the triglycerides were not significant although they decreased in most cases. They rose in five patients where the turbidity had fallen. On resumption of a normal diet the blood lipids rapidly returned to their control level. In some patients they rose temporarily to a higher level than that of the control period.

Blood-clotting and Fibrinolysis.—These were measured during the control period and at the end of the trial diet in 13 patients (Table VI). The Russell-viper-venom time for blood-clotting was abnormally shortened (accelerated) in five patients, two of whom had idiopathic hyperlipaemia. The fibrinolysis time was abnormally prolonged in six patients, only one of whom had idiopathic hyperlipaemia. Both abnormalities were present in three patients. At the end of the dietary period there was a significant lengthening of the venom

TABLE VI.—Effect of Corn-oil Diet on Russell-viper-venom Time and Fibrinolysis Time in 13 Patients

Case No.	Control Period			Dietary Period			Change at End of Diet		
	Venom Time (secs.)	Lysis Time (hrs.)	Plasma Turbidity Units	Venom Time (secs.)	Lysis Time (hrs.)	Plasma Turbidity Units	Venom Time (secs.)	Lysis Time (hrs.)	Plasma Turbidity Units
2	29	3.5	28	31	4.6	26	+2	+1.1	-2
4	34	6.4	23	53	4.9	20	+19	-1.5	-3
6	30	4.8	29	32	4.0	24	+2	-0.8	-5
7	28	2.4	27	33	2.4	25	+5	Nil	-2
8	28	2.6	27	31	1.6	23	+3	-1.0	-4
9	27	6.2	33	40	>7.0	26	+13	>+0.8	-7
12				43	4.3	105			
13	24	5.1	172	26	3.6	48	+2	-1.5	-124
14	18	3.8	37	17	2.7	72	-1	-1.1	+35
15	23	4.6	63	24	3.7	47	+1	-0.9	-16
16	17	2.9	156	20	2.9	98	+3	Nil	-58
17	21	>5.0	94	25	>6.0	116	+4		+22
18	25	2.8	172						
Mean	..	..	..	..	..	..	+5	-0.5	-15
S.E.	..	..	..	..	..	..	±1.8	±0.3	±12.9
P	..	..	..	..	..	..	0.05>	N.S.	N.S.

+, Lengthened. —, Shortened.

time by a mean of 5 seconds. The fibrinolysis time was shortened by greater than 0.1 hour in six patients, but this result was not significant. The blood lipids measured on the same day as these tests did not show any significant change, although the plasma turbidity was diminished in nine patients, all of whom showed lengthening of the venom time.

Discussion

There has been a great deal of study of the biochemical changes occurring as a result of dietary measures to lower the blood lipids. In the present trial the emphasis has been on the clinical response, although the biochemical and plethysmographic procedures were carried out by the same person in laboratories where similar aspects of this problem were being studied. Patients with familial hypercholesterolaemic xanthomatosis or idiopathic hyperlipaemia were selected because of the high incidence of atherosclerosis and the presence of xanthoma suitable for precise observation.

A diet was used in which the normal fats were replaced by an unsaturated fat (corn oil). An essential feature of the diet was that patients could carry on normally with as little restriction of their way of life as possible. In order to do this the unsaturated fat must be in an acceptable form and not as neat oil or in a

liquid feed as it is in metabolic experiments. The diet of "margarine," "milk," and "cheese" available contained a high proportion of corn oil, and the equivalent of 100 g./day of this was given.

The diet was well tolerated, for 18 patients thrived on it for three to four months. One other left after 19 weeks of treatment. It is desirable to have the help of a dietitian in constructing the diet. If one is not available the principle of a fat-free diet is well known and requires only the addition of corn-oil products in place of the customary fats. The only real disadvantage of the diet was absence of whole egg. This may be overcome by feeding chickens with meal containing sunflower oil to produce eggs rich in unsaturated fats, though recent work is less hopeful (Horlick and O'Neil, 1958, 1960).

Attempts have been made by others to lower the blood cholesterol by a fat-free diet. Severe restriction of fat produces only a moderate decrease in the blood cholesterol (Gordon, 1959) and in hypercholesterolaemic xanthomatosis the effect is not maintained and xanthomata are not affected (Borrie, 1957). In idiopathic hyperlipaemia the blood lipids may be lowered by a fat-free regime (Malmros *et al.*, 1954; Borrie 1957; Thannhauser, 1958) with a slow clearing of the xanthomata. Observation over a long period by Soffer and Murray (1954) showed that the blood lipid changes were transient. A fat-free diet is unpalatable, and it is difficult for the patient to accept such restriction for a long period. In view of this it is an unsatisfactory method of treatment.

So that a true measure of the effects, both clinical and biochemical, could be obtained it was necessary to observe each patient during a control as well as a treatment period. Xanthomata and atherosclerosis that have developed slowly are not likely to show dramatic changes in four to five months, but prevention of the progression of the disease may be possible.

The clinical response was encouraging, as xanthomata were often reduced in size. This change was definite in xanthoma tuberosum, where regression of the lesions may be complete. The more fibrous xanthoma tendinosum lesions were less affected, but in some cases they regressed or ceased to enlarge. If there is a change in the size of xanthomata it is probable that it is due to the removal of fat, and unlikely that fibrous tissue is affected. This is in accord with the greater effect on xanthoma tuberosum, which has a higher fat content than xanthoma tendinosum. Other authors have described change in xanthomata. Ahrens *et al.* (1957), in a metabolic ward experiment using corn oil, reported disappearance of the skin but no change in the tendon xanthomata. Malmros and Wigand (1957), using an out-patient diet, could show no regression. Skin xanthoma in patients with hyperlipaemia may respond to a low-fat diet alone (Soffer and Murray, 1954; Malmros *et al.*, 1954; Borrie, 1957).

In this study there was no good clinical evidence of improvement in atherosclerosis. Angina was not significantly altered. Half the patients with intermittent claudication improved clinically but without confirmatory plethysmographic findings. The observations were over a short period, and a longer trial will be required to prove or disprove the belief that the development or resolution of atherosclerosis can be influenced by dietetic control of the blood lipids.

Kuo *et al.* (1959) found that angina and claudication improved in patients with idiopathic hyperlipaemia on a

low-fat diet. These changes were prompt and occurred with a fall in the blood lipids. They believed that the effect was due to the fall in the blood triglycerides, with consequent improvement in oxygen diffusion in the tissues. These changes are due to alteration in the state of the blood and not to a change in the pathological conditions of the vessel wall.

The amount of fat in atherosclerotic lesions varies, but the content is high in arterial lesions found at necropsy in young people dying with hypercholesterolaemic xanthomatosis (Barr *et al.*, 1954). It is hopeful that changes in skin xanthomata were demonstrated in this trial, for it is possible that fat could be similarly removed from atherosclerotic lesions. Although this may be true in hypercholesterolaemic xanthomatosis it does not necessarily follow that the effect will be the same in atherosclerosis not associated with hypercholesterolaemia.

As a result of the diet with corn oil substituted for the normal fats the blood lipids, except the triglycerides, were significantly reduced. Although the total cholesterol did not always fall to normal the reduction was maintained so long as the diet continued. A greater fall could probably have been achieved if larger quantities of oil had been given, but this may well have made the diet unacceptable. Experimentally, substitution of corn oil to provide 40% of the calories of the diet has produced a similar drop of 20% or more in total cholesterol without alteration in the ratio of free to total cholesterol (Ahrens *et al.*, 1957; Malmros and Wigand, 1957).

Ahrens (1957) also found no consistent reduction of the triglycerides. In this trial the triglycerides rose in five patients, in whom the plasma turbidity fell. This suggests that the turbidity does not depend solely on the triglyceride content of the blood.

In the present investigation the venom or fibrinolysis time was abnormal in over half the patients examined. These abnormalities were present in both the patients with hypercholesterolaemic xanthomatosis and those with idiopathic hyperlipaemia. This differs from the finding of Nitzberg *et al.* (1959). They found in patients with idiopathic hyperlipaemia that the coagulation time by the venom technique was markedly shortened and the fibrinolysis time prolonged in the fasting state. There was some correlation between these tests and the serum triglycerides and lipaemia. In hypercholesterolaemic xanthomatosis they found that clotting and fibrinolysis were normal and there was no correlation between cholesterol and phospholipid levels.

There was lengthening of the venom time in six patients and shortening of the lysis time in six after treatment with the corn-oil diet. Peyman *et al.* (1960) found no alteration in the coagulation and fibrinolysis tests after long-term feeding of essential fatty acids. They did not restrict the normal fats of the diet and there was no reduction of the blood lipids. This may be the explanation of their negative findings. These tests of blood coagulation and fibrinolysis are artificial laboratory procedures, but the changes that have been found after treatment with a corn-oil diet would be expected to benefit the patient.

Summary and Conclusions

Fifteen patients with familial hypercholesterolaemic xanthomatosis and three with idiopathic hyperlipaemia were treated with a diet in which the normal fat was replaced by artificial "milk," "margarine," and

"cheese" containing a high proportion of an unsaturated fat (corn oil).

The diet was palatable and well tolerated. Unlike most previous metabolic ward studies, in the present one the patients continued at work. The treatment was maintained for four months and observations were made during a control period of similar length. There was significant depression of the blood cholesterol (free and total), phospholipids, and plasma turbidity. In some cases the triglycerides were also reduced. The xanthomata diminished, particularly xanthoma tuberosum, which often disappeared. The blood-clotting and fibrinolysis time was influenced in most cases in a way presumably beneficial to the patient.

There was no clinical or electrocardiographic evidence of an improvement in myocardial ischaemia in the six patients with angina. Symptoms decreased in three of the six patients with intermittent claudication, but there was no improvement in the peripheral circulation of the foot, measured by plethysmography. The trial was perhaps too short for such changes to be detected, and the treatment is being continued.

In the condition studied the incidence of atherosclerosis is high and the prognosis poor when myocardial ischaemia or peripheral vascular disease develops. Such a diet forms a practical method of treatment, and is worthy of trial in the hope of preventing further manifestations of atherosclerosis.

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ERYTHEMA NODOSUM

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"In erythema nodosum, many of the red patches are large and rounded. The central parts of them are very gradually elevated and on the 6th or 7th day, form hard and painful protuberances. From the 7th to the 10th, they constantly soften and subside without ulceration. On the 8th or 9th day, the red colour changes to bluish or livid, and the affected limb appears as if it had been severely bruised. This appearance remains for a week or ten days, when the cuticle begins to separate in scurf. The erythema nodosum usually affects the fore parts of the legs. I have only seen it in females, most of whom were servants. It is preceded by irregular shiverings, nausea, headache and fretfulness with a quick unequal pulse and a whitish fur on the tongue. These symptoms continue for a week or more, but they usually abate on the appearance of the erythema."—Robert Willan (1808).

The term "erythema nodosum" was introduced by Robert Willan, and the above description in his classic work *On Cutaneous Diseases*, published in parts between 1798 and 1808, is accompanied by a coloured illustration of the condition. He draws attention to the characteristic site, play of colours, and tenderness of the lesions; he refers to its predilection for females, and he underlines the constitutional upset which often precedes the rash. The description has not been bettered and is no less accurate to-day. We are still undecided